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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CALAMITA, HEATHER

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/626,096	UMEK ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 July 2000* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claims 49-51 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 49 is drawn to a method of detecting a target sequence using rolling circle amplification that incorporates ETM's into the target sequence as a means of detecting the presence of the sequence. The parent claim is drawn to detecting a target sequence using a hybridization complex that comprises a target sequence, capture probe, electrode and an ETM. Claim 49 incorporates the detection method outlined in the parent claim but does not further limit the scope of the invention.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43-47, 52-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Bamdad et al. (USPN 6,541,617 B1 04/01/2003).

Bamdad et al. teach a hybridization complex with a target sequence, a capture probe covalently attached to an electrode and an electron transfer moiety (ETM) with a redox potential (see whole document, especially col. 8 lines 8-21 and 55-62). They also teach determining the nucleotide at the detection position by detecting the ETM (see col. 8 lines 55-62). They teach the hybridization complex as having a label probe with a plurality of ETMs (see col. 45 lines 26-31, col. 55 lines 45-55). They additionally teach that hybridization complex with an extension primer hybridized to the target sequence

and contacting the complex with a polymerase enzyme and a plurality of NTPs each having an ETM covalently attached (see col. 7 lines 66-67, col. 8 lines 1-2, col. 67 lines 22-42). They teach the extension primer is extended by the polymerase to incorporate the ETM if one of the NTPs base pair with the base at the detection position of the sequence. They teach identifying the base by detecting the ETM. They also teach each NTP having an ETM with a different redox potential (see col. 67 lines 22-42). Furthermore, they teach forming a second hybridization complex comprising the first target sequence and an extension primer hybridized to the first target domain of the first target sequence, contacting the hybridization complex with a polymerase enzyme and a plurality of NTPs with covalently attached ETMs (see col. 67 lines 22-42). They teach extension of the primer by the polymerase to incorporate ETMs and form the first target sequence if one of the NTPs basepairs with the base at the detection position (see col. 67 lines 22-42). They teach the dissociation of the second hybridization complex and the contact of the first target sequence with the capture probe to form the first hybridization sequence (see col. 67 lines 22-42).

3. Claim 57 is rejected under 35 U.S.C. 102(b) as being anticipated by Meade et al. (USPN 6,177,250 01/23/2001).

Meade et al. teach providing an electrode with a covalently attached probe with a sequence substantially complementary to a first domain of a target sequence (see whole document, especially col. 9 lines 63-67 see col. 21 lines 59-60). They also teach a first and second label probe with first or second bases at the detection position of the target sequence (interrogation position). They teach a first and second ETM with first and second redox potentials respectively, forming a hybridization complex with the target sequence and determining the nucleotide at the detection position (see col. 7 lines 25-27, col. 21 lines 59-67, col. 22 lines 1-13).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 43-48, 50, 53-57 are rejected under 35 U.S.C. 102(e) as being anticipated by Blackburn et al. (USPN 6,686,150 B1).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Blackburn et al. teach a forming a hybridization complex with a first target sequence, a capture probe covalently attached to an electrode and a first ETM with a first redox potential (see whole document, especially col. 3 lines 42-46, col. 17 lines 51-56). They also teach forming the hybridization complex at two different temperatures (see col. 15 39-41). They further teach determining the nucleotide at the detection position by detecting the ETM (see col. 3 lines 42-46, and col. 17 lines 51-56). They teach a first target sequence having a target domain directly 5' adjacent to the detection position and the hybridization complex comprising the target sequence, capture probe and an extension primer hybridized to the first target domain of the target sequence (see col. 17 lines 28-56). Moreover they teach the capture probe serves as the extension primer (see col. 13 lines 66-67, col. 14 lines 1-6). They additionally, teach contacting a first hybridization complex with a polymerase enzyme and a plurality of NTPs that have ETMs covalently attached and identifying the base at the detection position by detecting the ETM (see col. 17 lines 28-56). They teach forming a second hybridization complex with the first target sequence, an extension primer hybridized to the first target domain of the first target sequence and

contacting the second hybridization complex with a polymerase and a plurality of NTPs each with a covalently attached ETM (see col. 3 lines 36-49). They further teach if one of the NTP's basepairs with the base at the detection position the extension primer is extended by the polymerase to incorporate the ETM and form the first target sequence (col. 3 lines 36-49). They teach disassociate second hybridization complex and contact the first target sequence with the capture probe to form the first hybridization complex (see col. 3 lines 36-49). Additionally, Blackburn et al. teach a target sequence with a first target domain having a detection position and a second target domain adjacent to the detection position (see col. 22 lines 38-57). They teach hybridizing a second ligation probe to a second target domain, hybridizing a first ligation probe to a first target domain and forming a ligation structure if the first ligation probe has a base that is perfectly complementary to the detection position (see col. 22 lines 38-57). They teach a ligation enzyme that ligates the first and second ligation probes of the ligation structure to form a ligated probe and forming an assay complex with the ligated probe, a capture probe covalently attached to an electrode and at least one ETM (see col. 22 lines 38-57). Blackburn et al. teach detecting the presence or absence of the ETM as an indication of the ligation structure formation and identifying the base at the detection position (see col. 22 lines 38-57). They also teach the hybridization complex having a label probe with a first base at a detection position and an ETM with a first redox potential and they teach a label probe with a plurality of first ETMs (see col. 7 lines 20-24, Fig 16C). They teach an electrode with a covalently attached capture probe with a sequence substantially complementary to a first domain of a target sequence and a first label probe with a first base at the detection position of the target sequence and a first ETM with a first redox potential. They also teach a second label probe with a second base at the detection position of the target sequence and a second ETM with a second redox potential, forming a hybridization complex with the target sequence and one of the label probes and the capture probe, and determining the nucleotide at the detection position (see col. 7 lines 44-46, Fig 16H).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bamdad et al. (USPN 6,541,617 B1 04/01/2003) in view of Meade et al. (USPN 6,177,250 01/23/2001).

The teachings of Bamdad et al. are described previously.

Bamdad et al. do not teach forming the hybridization complex with the target sequence at two different temperatures.

Meade et al. do teach forming a hybridization complex of probes and a target sequence at two different temperatures (see col. 11 lines 40-45).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Meade's method of using two different hybridization temperatures with Bamdad's method for detecting specific nucleic acid sequences and target analytes in order to detect a greater range of target analytes and sequences. Meade et al. state a variety of hybridization conditions may be used in hybridizing a probe to a target sequence. As the hybridization conditions are altered so is the stringency of the binding of the probe to the target sequence or analyte (col. 11 lines 40-45). It would have been prima facie obvious to apply Meade's hybridization conditions to Bamdad's hybridization complex to achieve the expected advantage of detecting a greater range of target sequences or analytes by altering the hybridization conditions when forming the complex .

6. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ullman et al. (USPN 5,185,243 02/09/1993) in view of Meade et al. (USPN 6,177,250 01/23/2001).

Ullman et al. teach hybridizing a second ligation probe to a second target domain, hybridizing a first ligation probe to the first target domain, and if the first ligation probe is perfectly complementary to the detection position a ligation structure is formed. They also teach a ligation enzyme that ligates the first and second ligation probes of the ligation structure to form a ligated probe, forming an assay complex with the ligated probe. They also teach detecting the presence or absence of a reporter as an indication of the formation of the ligation structure and identifying the base at the detection position (see whole document, especially col. 28 lines 4-56).

Ullman et al. do not teach using an ETM as the reporter.

Meade et al. do teach using an ETM as a reporter or label for oligonucleotides (see col. 5 lines 29-38).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Meade's method of modifying nucleic acids at specific sites with redox active moieties or labels with Ullman's method for detecting specific nucleic acid sequences using ligation chain reaction in order to create a nucleic acid modified with a covalent label at a predetermined position. Meade et al. state it is desirable to provide a nucleic acid with a covalent label at a predetermined position that causes negligible perturbations of the structure and retains its ability to base pair normally (see col. 5 lines 20-23). It would have been prima facie obvious to apply Meade's labels to Ullman's method for detecting specific nucleic acid sequences using a technique which amplifies the signal from a labeled nucleotide to achieve the expected advantage of creating a nucleic acid with a covalent label at a predetermined position that causes negligible perturbations of the structure and retains its ability to base pair normally. This is advantageous because the specificity of LCR is such that only oligonucleotides which hybridize without mismatch at their junction are ligated. This requirement for exact base pairing can be used to discriminate single base differences in a target sequence.

7. Claims 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banér et al. (*Nucleic Acids Res.* 26:5073-5078, 1998) in view of Meade et al. (USPN 6,177,250 01/23/2001).

Banér et al. teach providing a rolling circle probe using a first ligation sequence substantially complementary to a first domain of the target sequence, a second ligation sequence substantially complementary to a second domain of a target sequence and a priming sequence. They also teach hybridizing the first ligation sequence to the first domain and the second ligation sequence to the second domain to make a first hybridization complex. They teach ligating the first and second ligation sequences together and adding a primer complementary to the priming sequence, a polymerase and NTPs. They teach detecting a radiolabel as and indicator of the presence of a target sequence (see whole document, especially p. 5074 col. 1 paragraphs 2 and 3 and Figure legend 1).

Banér et al. do not teach using ETM as the reporter or label. They also do not teach using a nucleotide analog.

Meade et al. do teach using an ETM as a reporter or label for oligonucleotides or nucleotide analogs (see col. 5 lines 29-38, col. 6 lines 5-7).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Meade's method of modifying nucleic acids and analogs at specific sites with redox active moieties or labels with Banér's method for amplifying the signal of padlock probes with rolling circle replication in order to create a nucleic acid probe with a covalently attached label that does not interfere with the ability of the probe to bind the target nucleic acid sequence. Meade et al. state it is desirable to provide a nucleic acid with a covalent label at a predetermined position that causes negligible perturbations of the structure and retains its ability to base pair normally (see col. 5 lines 20-23). It would have been prima facie obvious to apply Meade's labels to Banér's method for analyzing gene sequence variants using padlock probes and rolling circle replication to achieve the expected advantage of having a label which can be covalently attached to a nucleic acid at a predetermined position and allow for retention of

its ability to base pair normally. This is advantageous because the ETM label enhances the ability of rolling circle replication to amplify detection signals of reacted probes. The specificity of the probe for the target sequence is paramount to accurate signal amplification and detection. Therefore it important to have a label that does not interfere with accurate base pairing during hybridization of the probe to the target sequence.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 49-51are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 9-10 of U.S. Patent No. 6,686,150 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 49-51 of the instant application are drawn to a method for detecting a target sequence providing a rolling circle probe comprising a first ligation sequence substantially complementary to a first domain of the target sequence, a second ligation sequence substantially complementary to a second domain of the target sequence and a priming sequence, hybridizing the first ligation sequence to the first domain and second ligaiton sequence to the second domain to form a first hybridization complex, ligating the first and second sequences together and adding to the sequences a primer substantially complementary to the priming

sequence, a polymerase, NTP;s and an ETM to form a rolling circle concatamer with at least one covalently attached ETM. The RCP has at least one nucleotide analog and the primer hybridizes both to the target sequence and the priming sequence. Claims 1, 9-10 of USPN 6,686,150 B1are also drawn to a method for detecting a target sequence providing a rolling circle probe comprising a first ligation sequence substantially complementary to a first domain of the target sequence, a second ligation sequence substantially complementary to a second domain of the target sequence and a priming sequence, hybridizing the first ligation sequence to the first domain and second ligaiton sequence to the second domain to form a first hybridization complex, ligating the first and second sequences together and adding to the sequences a primer substantially complementary to the priming sequence, a polymerase, NTP;s and an ETM to form a rolling circle concatamer with at least one covalently attached ETM. The RCP has at least one nucleotide analog and the primer hybridizes both to the target sequence and the priming sequence. In the instant application the small variation in the method steps does not render the invention unobvious in the overall design when compared to USPN 6,027,945.

Summary

10. No claims are allowed.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita, Ph.D. whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on weekdays 7:30 A.M. - 4:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571.272.0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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